JOURNAL OF CLINICAL MICROBIOLOGY, Apr. 1994, p. 1043–1049
0095-1137/94/$04.00+0

Vol. 32, No. 4

Animal and Public Health Implications of Gastric Colonization of Cats by *Helicobacter*-Like Organisms

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Received 27 October 1993/Returned for modification 2 December 1993/Accepted 11 January 1994

The bacterial genus *Helicobacter* contains a number of species which colonize the gastric mucosa of mammals. Natural and/or experimental gastric pathology has been correlated with colonization in humans and a wide variety of animal species. Historical reports in the literature suggest that a high percentage of cats are colonized by large, spiral, gastric helicobacter-like organisms (GHLOs). One of these bacteria (*Helicobacter felis*) has been isolated on artificial media and has experimentally caused gastritis in gnotobiotic dogs. This study surveyed the prevalence of helicobacter colonization in random-source cats by using the urease assay. Histologic examination was performed to determine the degree of associated pathology present. GHLOs associated with chronic gastritis were present in 70% of the juvenile and 97% of the adult cats studied. Although further study is needed to determine specifically what role GHLOs play in feline gastrointestinal disease, these results indicate that helicobacter colonization should be considered in the pathogenesis of feline gastroenteropathy. Furthermore, the high prevalence of feline infection is interesting because cats have recently been implicated as a potential reservoir for human infection by helicobacter-like organisms.

The last decade has seen a major change in thinking in regard to the contribution of bacteria to gastric pathology in humans (43). There are now 10 species included in the newly created genus *Helicobacter*, the majority of which, through evolutionary adaptations, have become efficient colonizers of mammalian stomachs (2, 29, 53). Many of these organisms share a characteristic large, spiral morphology and have historically been described in animals as gastric "spirilla" (57). The classical view that a euchlorhydric stomach is a predominately sterile organ protected from bacterial colonization by low pH has been disproven in recent years. The most frequent human gastric colonizer, *Helicobacter pylori*, is now known as the major cause of gastritis in the human population (29). *H. pylori* infects 20 to 90% of adult populations and is believed to play a major role in the pathophysiology of duodenal and gastric ulcers and to be a risk factor for gastric neoplasia (19, 29, 54). One of the first species identified as a member of the *Helicobacter* genus was *H. felis*, a "spirillum" originally isolated from a cat stomach but shown to colonize dogs as well (40). Gastritis caused by experimental infection of gnotobiotic dogs with *H. felis* has been reported (41), and lesions potentially caused by helicobacter infection of cats have been briefly described (32).

Recently, it has been discovered that a small subset of human gastritis cases were not caused by *H. pylori* but by other gastric helicobacter-like organisms (GHLOs) which are morphologically identical to the spirilla found in animals. It has been suggested that domestic animals may serve as a reservoir for human infection (33, 37, 45). To define the potential role of *Helicobacter* spp. in feline disease and as potential zoonotic agents, we characterized the gastric helicobacter colonization in a group of juvenile and adult cats by using methods previously applied to other species. Stomach tissues were then evaluated for possible associations between GHLO colonization and histologic changes.

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MATERIALS AND METHODS

Animals. Stomach tissues were obtained immediately postmortem from a group of 55 random-source cats which were humanely euthanized at an animal shelter. The animals were classified as immature animals (animals less than or equal to 20 weeks of age; $n = 23$) or adults (animals over 20 weeks of age; $n = 32$) by comparing morphologic features with animals whose ages were known.

Urease assay. To determine the distribution and density of bacterial colonization in the excised stomachs, a mucosal urease mapping assay was performed (22). Stomachs were opened along the greater curvature and laid flat to facilitate manipulation. Ingesta were removed, and the mucosal surface was gently washed with three changes of sterile saline. A 4-mm-diameter punch was used to cut full-thickness samples of gastric tissues at 16 predetermined sites from each stomach (Fig. 1). Samples obtained in this fashion were placed into individual wells of a plastic microtiter tray, and 0.2 ml of urease test solution was added to each well by a previously published method (31). The test reagent was a buffered solution containing a substrate (urea), a pH indicator (phenol red), and a preservative (sodium azide) to eliminate the possibility of false-positive reactions due to growth of urease-positive contaminants during incubation. The assay plates were visually monitored constantly for the first 8 h and then intermittently for a total of 48 h. Any well which showed a color change of the pH indicator to a deep pink was considered to be positive. The elapsed time from placement of the sample in the well to development of a positive reaction was recorded, and any

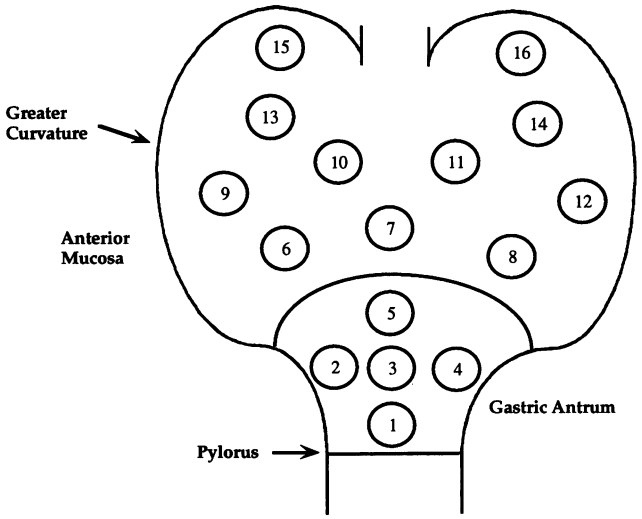

FIG. 1. Schematic drawing of a cat stomach showing the tissue sample sites used for the urease assay.

samples that had not turned color within 48 h were recorded as negative.

Since the rapidity of positive color development in the mucosal urease assay is proportional to the density of colonization by urease-positive helicobacters, it is possible to use these data to obtain a semiquantitative measure of the relative distribution of the organisms throughout the gastric mucosa (41). For this purpose, a value defined as the colonization factor was determined for each urease site in the immature and adult groups by dividing the sum of the reciprocal of the times recorded for urease positivity (in minutes) by the number of animals in each group and multiplying by 1,000. For this calculation, the reciprocal of a negative urease assay result (no color change at 48 h) was considered to be zero.

Histology. After fresh tissue samples were removed for the urease assay, the remainder of the stomach was fixed in Lillies' neutral buffered formalin or in Karnovsky's fixative. Selected portions of formalin-fixed tissues were embedded in paraffin, sectioned by standard methods, and stained by the hematoxylin-and-eosin or modified Warthin-Starry technique. Semithin (0.5-mm) and thin (50- to 70-nm) sections were resin embedded and sectioned as previously described (11). Semithin sections were stained with methylene blue (containing 1% borax) for light microscopy, and thin sections were stained with uranyl acetate and lead citrate for transmission electron microscopy.

RESULTS

Urease assay. Eight-six percent of the cats in this study had evidence of helicobacter colonization based on urease assay results (Table 1). Although almost a third of the juvenile cats were negative at all sites, nearly all adults were positive at four or more sites. This age-related increase in colonization resulted in a statistically significant difference (χ^2 analysis; $P < 0.01$) between the number of immature and mature animals found in the negative, sparsely (more than four sites) positive, and broadly positive groups.

The distribution of urease activity on the basis of gastric topology is depicted in Fig. 2. The colonization factor (roughly proportional to the number of urease-positive organisms) was higher at every site in adult animals than in juvenile cats, a finding which is also consistent with an age-related increase in colonization. In both groups of animals, colonization was higher in the body of the stomach and the transitional area between the body and the antrum than in the terminal antrum.

TABLE 1. Prevalence of *Helicobacter*-like organism colonization in cats

Group (no. of cats)	No. (%) of cats		
	Urease negative	<4 sites positive	≥4 sites positive
Juveniles (23)	7 (30)	5 (22)	11 (48)
Adults (32)	1 (3)	1 (3)	30 (94)
Total (55)	8 (14)	6 (11)	41 (75)

Presence of organisms. The presence or absence of organisms possessing characteristics morphologically consistent with GHLOs was assessed on Warthin-Starry-stained sections. Large, spiral, argyrophilic bacteria were evident in gastric sections showing positive urease scores but were sparse or nonexistent in urease-negative areas (data not shown). Representative light and electron photomicrographs of colonized epithelium are shown in Fig. 3 and 4. Organisms were not directly adherent to gastric epithelium but on occasion were found within the canaliculi or cytoplasm of viable parietal cells, as described in previous reports (32, 41, 42, 57).

Correlation between colonization and pathology. A scoring system was utilized to simplify comparisons between animals and to attempt to identify a correlation between colonization and gastritis. Fifteen representative animals (seven immature animals and eight adults) were selected on the basis of previously determined urease results to represent a range of colonization density. The single fastest positive urease reaction time from the antrum (sites 1 to 5) and from the body (sites 6 to 16) of each animal was used to give each anatomical region a urease score based on the following criteria: −, no reaction within 24 h; +, positive reaction at 8 to 24 h; ++, positive reaction at 2 to 8 h; +++, positive reaction at <2 h.

The presence of histological changes in the stomachs was determined by microscopic evaluation of hematoxylin-and-eosin-stained slides from the 15 animals, which was performed in a blinded fashion. Histologic findings ranged from normal

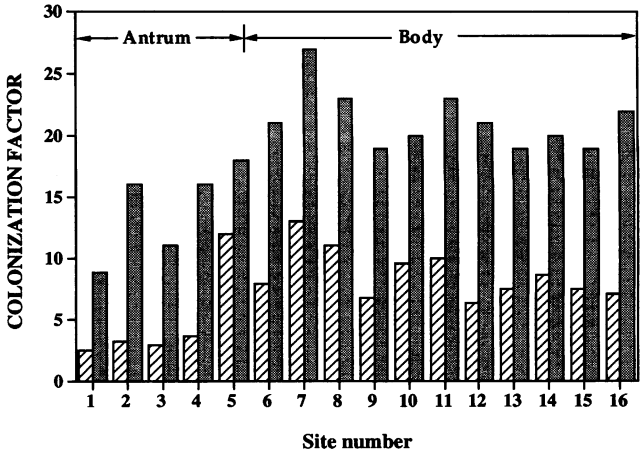

FIG. 2. Relative distribution of urease-positive organisms throughout the stomachs of juvenile (▨) and adult (▩) cats (see text).

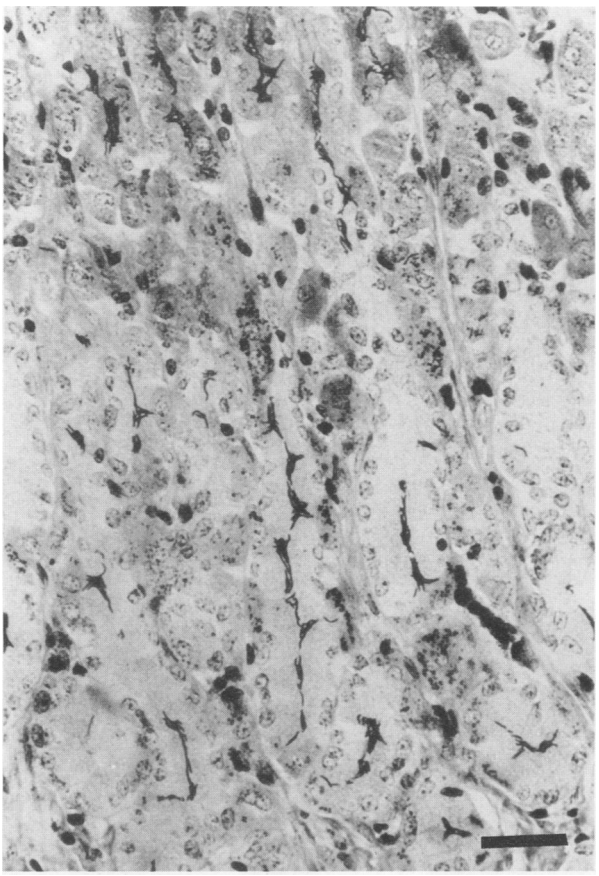

FIG. 3. Gastric mucosa of a cat heavily colonized with GHLOs. At this magnification, the bacteria appear as black filamentous organisms (Warthin-Starry staining; bar, 30 μm).

mucosa to various degrees of gastritis. To grade the differences between animals, the level of inflammation was scored on the basis of the following features: −, small numbers of lymphocytes and a few neutrophils and eosinophils scattered throughout the subglandular region of the mucosa; +, mild, relatively diffuse infiltrate of lymphocytes and small numbers of neutrophils and eosinophils present in the subglandular region with small, focal extensions of these cell infiltrates extending toward the luminal surface; ++, mild, relatively diffuse mixed leukocytic infiltrates present in the subglandular region with focal aggregates of leukocytes composed primarily of lymphocytes concentrated in the subglandular region with focal extension through the lamina propria toward the luminal surface and into the underlying mucosa; +++, mild, relatively diffuse, mixed subglandular leukocytic infiltrates arranged as multiple lymphoid nodules that focally displaced most of the glands through the full thickness of the mucosa and/or as focal extensions of leukocytes from the subglandular region into the lamina propria and submucosa. The focal cellular aggregates were a mixture of lymphocytes and plasma cells with some polymorphonuclear leukocytes in the lamina propria at the level of the gastric pits.

Histology and urease scores are tabulated in Table 2. Only two immature cats had significant gastric pathology, and these were the animals with the highest urease scores. The most marked gastritis was observed in the antra of mature animals heavily colonized by GHLOs as indicated by concurrent strong urease reactions in the antrum or body. Representative areas of pathology are shown in Fig. 5 and 6. The observed association between colonization and histologic changes strongly suggests a causal role for the bacteria.

DISCUSSION

Since the turn of the century there have been reports that the stomachs of domestic carnivores were colonized with large, spiral bacteria (4, 42). The contemporary cat population we studied had a high prevalence of colonization which increased with age, a finding in agreement with a previous report (35). This rapid, age-related increase in prevalence is consistent with a model whereby cats are exposed to an infectious dose of organisms early in life and, once established, the infection persists for life. Lifelong infection also occurs in ferrets colonized with *H. mustelae* and in humans colonized with *H. pylori* (20, 54).

Two commonly found morphologic types of spiral bacteria are present in cats and dogs. One is *H. felis*, which has been isolated on artificial media and is distinguished by the presence of characteristic periplasmic fibrils (40, 50). The other helical organism has no fibrils and has not been cultured, although it has been maintained by infecting the stomachs of carrier mice (11). Bacteria morphologically identical to the latter bacterium have been described in humans, nonhuman primates, pigs, and cheetahs (13, 16, 17, 45, 46). Although originally designated "*Gastrospirillum hominis*" or a gastrospirillum-like organism, the name "*Helicobacter heilmannii*" has been proposed on the basis of a genetic analysis which placed the organism in the genus *Helicobacter* (53). In the present study, the only form visualized with electron microscopy was morphologically consistent with "*H. heilmannii*," although *H. felis* was likely to be present as well, since mixed infections are common (40).

Results of urease mapping in this study revealed the heaviest helicobacter colonization in the acid-secreting fundic mucosa of the stomach, an area rich in parietal cells. In contrast, when *H. felis* is introduced into germ-free rats the resulting colonization is relatively poor in the fundus (23). This suggests that host-specific factors are involved, and one possible mechanism that has been described is the ability of some helicobacters to inhibit the secretory function of parietal cells directly (7, 56).

The pathogenic potential of gastric spirilla was discussed in some early reports, and veterinary textbooks written as recently as the late 1950s mentioned these organisms as possible etiologic agents of clinical and/or histologic gastritis in small animals (8). However, this possibility has been generally ignored as recent advances in gastroenterology focused on the "no acid, no ulcer" theory of ulcer disease, the use of cimetidine and other antisecretory agents, and the effects of NSAIDS on the gastric epithelium (47). We believe that the contribution of gastric bacteria to feline and canine gastroenteropathies should be revisited.

Helicobacter infection is consistently correlated with gastritis in natural or experimental infection of a wide variety of animal species (3, 6, 16, 17, 22, 23, 33, 38, 41, 46, 48, 51). The most consistent histologic change associated with gastric colonization in animals is a multifocal lymphocytic infiltrate which often forms lymphoid follicles, a type of chronic gastritis previously described in natural or experimental helicobacter infection in dogs and ferrets (20, 22, 28, 34, 41). A very similar histologic pattern occurred in the cats in our study, as well as in those examined by Heilmann and Borchard (32).

Symptomatic gastritis is a frequent finding in carnivores, and the potential role of gastric helicobacters should be considered. Although the lack of historical information regarding the cats utilized in this study makes it impossible to address the

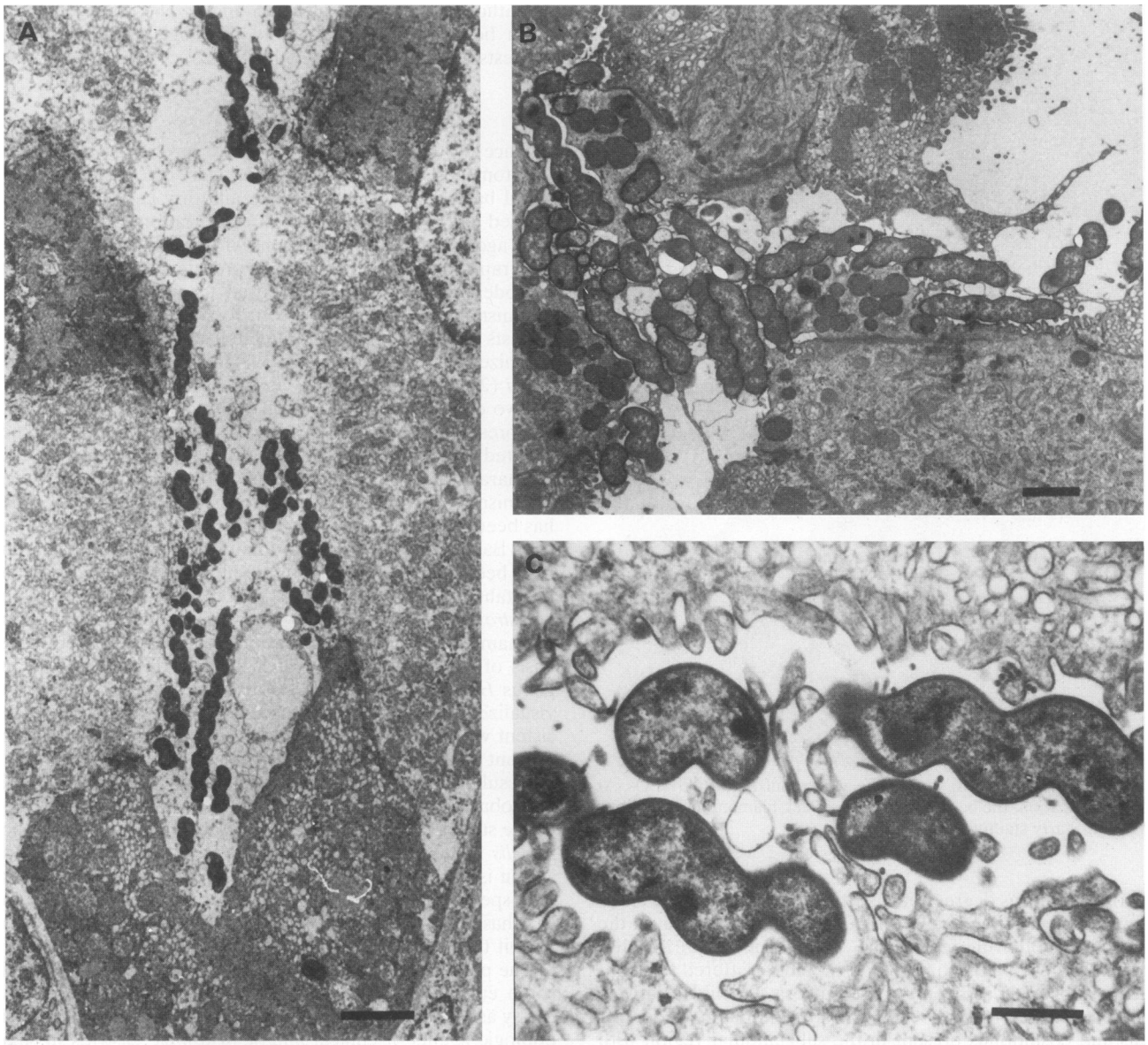

FIG. 4. Transmission electron micrograph of gastric tissue from a cat showing the presence of large numbers of tight, helix-shaped bacteria resembling "*H. heilmannii*" in the gastric pits (A and B) and in close proximity to parietal cells (C). Bars, 2, 1, and 0.5 μm in panels A, B, and C, respectively.

issue of clinical signs, other reports have raised the possibility of disease caused by helicobacters in domestic and exotic felines. In one recent study, a group of Persian cats affected by severe chronic gastritis were found to be heavily colonized by "*H. heilmannii*"-like bacteria, and since no other etiologies were identified the investigators speculated that helicobacters might have caused the lesions and signs (18). Helicobacters have also been implicated as the cause of an epizootic of clinical gastritis in captive cheetahs (17). Examination of gastric tissues from affected animals revealed three morphologic types of spiral bacteria, one consistent with "*H. heilmannii*," one with helical filaments similar to those of *H. felis*, and one that possesses similarities to *H. pylori*. The investigators were able to isolate the *H. pylori*-like organism, and on the basis of further characterization they have proposed the name "*Helicobacter acinonyx*" (15). Experimental transmission of the helicobacters from cheetahs to mice and domestic kittens resulted in lesions consistent with chronic gastritis, suggesting a causal role (16).

Although further studies are needed to characterize the host response to helicobacters, some findings can be discussed in the context of existing data. Moderate numbers of eosinophils were found in colonized stomachs in this study, and although other causes were not excluded, we believe that bacterial infection should be considered when eosinophils are present in the gastric mucosa of small animals. Indeed, eosinophils have been found to be a major component of the inflammatory response to helicobacters in some human and animal cases, especially during the acute phase of infection (23, 24, 26, 38, 41, 44, 51, 52). The presence of lymphoid nodules has historically been considered a normal histologic finding in descriptions of the gastric mucosal architecture of dogs and cats (1),

TABLE 2. Results of urease assay and histologic examination of cat stomachs[a]

Cat group and individual designation	Urease score		Gastritis score	
	Fundus	Antrum	Fundus	Antrum
Immature				
J	−		−	−
N	−	−	+	−
L	−	−	−	+
M	+	−	ND[b]	−
K	+	+	−	−
A	+	++	++	++
O	++	++	−	+++
Adult				
E	++	++	++	++
G	+++	+	+	+++
B	+++	+++	++	ND
C	+++	+++	++	++
D	+++	+++	+	+++
F	+++	++	+	+++
H	+++	+++	+	+++
I	+++	+++	++	+

[a] Scoring was performed as described in Results.
[b] ND, not done.

but we suggest that these are areas of host response to helicobacter antigens. Gastric ulcers were not seen in the cats we examined, but helicobacter involvement may also need to be considered in cases of gastric or duodenal ulcers, since *H. pylori* is known to be involved in ulcerogenesis in humans and *H. mustelae* has been identified in ulcerative lesions in ferrets (20).

The route of transmission for members of the genus *Helicobacter* is not entirely understood. Fecal-oral transmission would be a logical assumption, but helicobacters have only rarely been cultured from the stool of infected humans or animals. *H. mustelae* in ferrets is an exception, and it has been shown that spontaneous or induced hypochlorhydria increases the shedding of viable helicobacters in ferret feces (21, 25), a fact that is intriguing since helicobacters have been shown to cause transient hypochlorhydria in humans and animals (24, 41, 51, 54). The very rapid (mean, 3 h) gastrointestinal transit time (5) of ferrets may be involved as well. A recent study documented *H. pylori* isolation from human feces in a high-prevalence third-world population, suggesting that this route is important in developing countries (55). However, results from experimental studies with rats and mice have shown that fecal-oral transmission is difficult under some circumstances, suggesting that the oral-oral route of transmission is important (39). This view is supported by epidemiologic studies which have documented *H. pylori* transmission in humans by exposure to gastric secretions (54) and improper disinfection of endoscopes and pH probes (36, 54). These reports highlight the possibility that helicobacter infections are nosocomial in human or animal health care facilities.

Large spiral helicobacters ("*H. heilmannii*," "*G. hominis*," or gastrospirillum-like organisms) colonize most dogs and cats and a small subset of the human population. Since no environmental source of these helicobacters has been documented, it has been suggested that human infection is zoonotic (33, 37, 45). Two patients in one series of "*H. heilmannii*" or "*G. hominis*" case reports had close contact with pets—one lived with 14 cats, and the other had two Irish setters in the household (14). Since the organism has not been cultured, it is difficult to compare isolates from humans with those from pets. However, ultrastructural examination of helicobacter-like organisms from one recent human case revealed periplasmic fibrils, a characteristic which has previously been identified only in *H. felis* isolated from dogs and cats (58). Zoonotic transmission from domestic pets to humans should be considered part of the epidemiology of helicobacter infections, but such transmission is likely a rare event considering the large numbers of infected animals and the relative paucity of human cases.

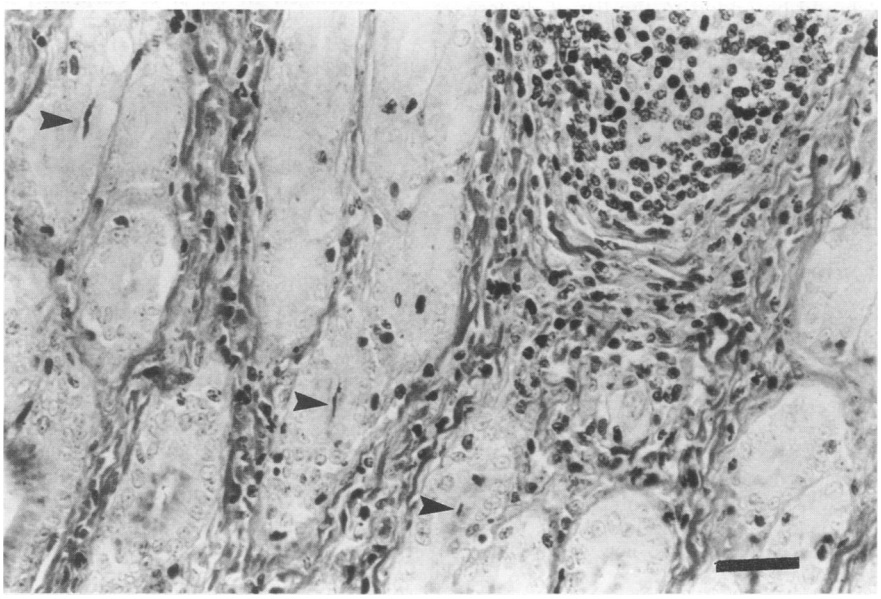

FIG. 5. Focus of chronic inflammatory cells present in the gastric mucosa of a cat colonized with GHLOs (arrowheads) (Warthin-Starry staining; bar, 30 μm).

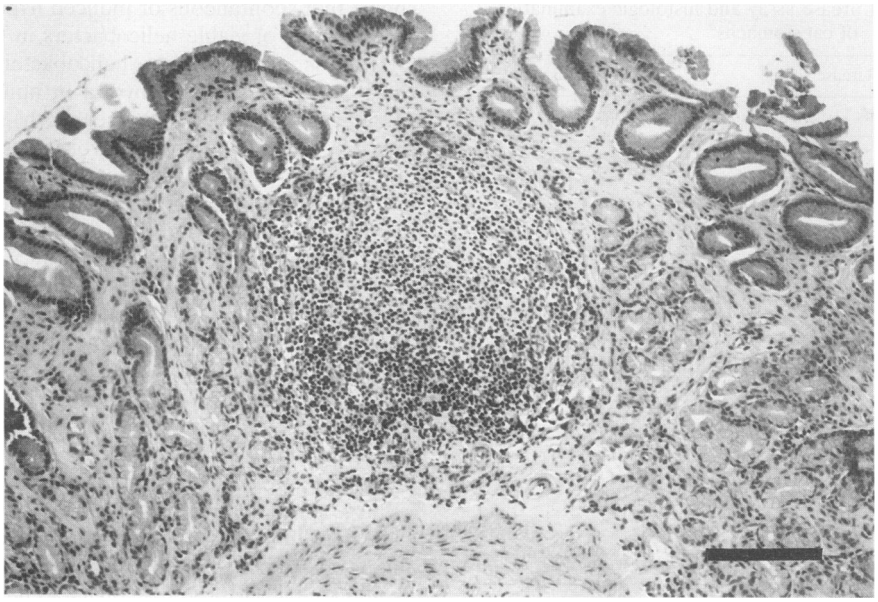

FIG. 6. Photomicrograph depicting a lymphoid nodule in the antral mucosa of a cat colonized by GHLOs (hematoxylin-and-eosin staining; bar, 200 μm).

Should antimicrobial therapy be considered for cases of feline gastritis or ulcer disease? Combination antibiotic regimens involving metronidazole, bismuth, and either amoxicillin or tetracycline have been used to treat natural and experimental helicobacter infections in humans and animals (12, 27, 49). Therapy will not be indicated until more is known about feline helicobacter infection, but preliminary studies suggest that similar regimens may be effective in reducing colonization of feline stomachs (40). It is interesting that bismuth compounds and metronidazole have been used with some success for empirical therapy of previously undiagnosed gastrointestinal syndromes in dogs and cats.

In conclusion, we believe that there are a number of issues to be considered regarding feline helicobacter colonization. (i) Helicobacter infection should be added to the list of disease entities which have been associated with chronic gastritis in cats (9, 10, 30). (ii) GHLO infection may need to be considered a cause of symptomatic illness. (iii) Cats are a potential reservoir for the zoonotic spread of helicobacters. In this study we validated a number of techniques for evaluation of the helicobacter status of cats, and it is expected that future studies will further define the relative impact of *Helicobacter* spp. on domestic feline health and disease.

ACKNOWLEDGMENTS

This study was supported in part by the National Health and Medical Research Council of Australia; Public Health Service grants RR01046 and T32-RR07036 from the Division of Research Resources, National Institutes of Health; and grants P01-CA28842 and P01-CA-26731 from the National Cancer Institute.

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